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REMARKS

Claims 1-5, 7, 8, 16-33 and 66-77 are pending.
Claims 1, 3, 18, 23 and 24 have been amended above. Support for the amendment to claim 1, to recite "procaryotic cell or a filamentous bacteriophage," can be found throughout the specification. Specifically, support can be found, for example, on page 3, lines 8-9; page 4, lines 19-21, and page 6, lines 25-35, describing heteromeric receptors expressed on the surface of cells and filamentous bacteriophage.

Claim 1 has been amended to recite "first and second polypeptides which form functional heteromeric receptors." Support for the amendment can be found throughout the specification. Specifically, support can be found, for example, on page 6, lines 9-10; page 7, lines 1-4, and page 10, lines 26-30, which describe functional heteromeric receptors including immunoglobulins.

Claim 1 has been amended to substitute the word "procaryote" for the word "prokaryote." Both words are synonymous and the change is made for consistency with the spelling of the word used in the specification. Claims 3, 18 and 23 have each been amended to add the word "are" which corrects an obvious typographical error.

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Claim 24 has been amended to recite that the DNA sequences encode a fusion protein. Support for this amendment can be found throughout the specification. Specifically, support can be found, for example, on page 2, lines 28-30; page 7, lines 10-12, and page 10, lines 1-5, describing DNA that encodes proteins including antibody fragments and fusion proteins. Accordingly the amendments do not introduce new matter and entry thereof is respectfully requested.

Applicant would like to thank the Examiner for calling attention to the informalities in the drawing numbering. Applicant respectfully submits that the requested changes to drawing numbering will not alter the substantive prosecution of the application and respectfully requests that these grounds of rejection be deferred until there is an indication of allowable subject matter in the above-identified application.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-5, 7, and 77 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The Office Action contends that the specification describes methods for expression of gVIII fusions on the surface of M13. The Office Action alleges that sufficient guidance is not provided in the specification to enable one skilled in the art to express gVIII

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fusion proteins on the surface of a cell. In support of this rejection, the Office Action cites several examples where the specification describes expression of gVIII fusions on the surface of M13.

Applicant respectfully traverses the rejection and maintains that the specification enables functional heteromeric receptors expressed as gVIII fusions on the surface of a procaryotic cell. For example, on page 3, lines 8-9, the summary of the invention describes "heteromeric receptors being expressed on the surface of a cell." Further support can be found on page 4, lines 19-21, which describes receptors that "can be expressed on the surface of cells such as those producing filamentous bacteriophage." Therefore, the specification describes that gVIII fusion proteins of the invention can be expressed on the surface of procaryotic cells.

Moreover, the specification teaches and provides sufficient guidance for the construction of a DNA encoding a gVIII fusion protein expressed on the surface of a procaryotic cell. Specifically, such teachings and guidance can be found, for example, on page 7, line 1, through page 11, where the specification exemplifies the use of gVIII coat protein as an anchor for the fusion protein on the cell surface and the attachment of the encoding nucleic acid to a leader sequence to direct the fusion protein to the surface of a procaryotic cell. The specification provides additional teachings and guidance for the expression of fusion proteins in its description of

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exemplified vectors set forth, for example, on page 11, line 33 through page 12, line 28. Additionally, on pages 29-33, and particularly on page 32, lines 23-30, the specification describes the construction and screening of surface expression libraries. Throughout these teachings are numerous descriptions of the procaryotic cell libraries which produce the bacteriophage of the invention. These surface expression libraries consist of procaryotic cells having the gVIII fusion proteins of the invention because they are host to the filamentous bacteriophage of the invention, which also have the gVIII fusion proteins of the invention expressed on their surface. Therefore, the application describes and exemplifies procaryotic cells having functional heteromeric receptors expressed as gVIII fusion proteins on their cell surface.

Further, one skilled in the art knows that the methods taught in the specification for expression of gVIII fusion products results in the production of fusion proteins on the surface of a procaryotic cell. As described above, the gVIII product initially resides on the surface of its host procaryotic cell. The gVIII coat protein gets incorporated into the phage when it buds off of the bacteria, taking a portion of the bacteria cell membrane with it as a component of its coat. This arrangement is well known in the art as shown in Exhibits A and B. Briefly, Exhibit A, Marvin and Wachtel, "Structure and assembly of filamentous bacterial viruses" in Nature Vol. 253 pp. 19-23 (1975), describes, in part, the life cycle of a filamentous bacteriophage where a diagram of the bacteriophage life cycle is shown in Figure 1 on page 20. This diagram shows coat proteins,

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including the gVIII product, anchored on the cell surface via membrane anchoring as well as via the attached phage particle. Additionally, attached as Exhibit B, Wilson and Finlay, "Phage display: applications, innovations, and issues in phage and host biology" Canadian Journal of Microbiology vol. 44 (1998), is a recent review which corroborates that known at the time of filing, namely, that gVIII is first inserted into the procaryotic host cell membrane of filamentous bacteriophage prior to phage assembly. In this regard, page 316, (first column, lines 4-7, second paragraph) states that "Although pIII and pVIII are synthesized with N-terminal signal peptides that are cleaved upon membrane insertion, they remain anchored in the membrane by C-terminal hydrophobic regions with their N-termini in the periplasm." In light of that which was well known in the art in regard to the life cycle and assembly of filamentous bacteriophage from procaryotic host cells, together with the teachings and guidance in the application, Applicant maintains that the specification provides sufficient description to enable expression of gVIII fusion products on the surface of the procaryotic cell. Accordingly, Applicant respectfully requests that rejection of claims 1-5, 7, and 77 under 35 U.S.C. § 112, first paragraph be withdrawn.

Claims 1-4, 7, 16-19, 21-29, 31, 32, 66-75, and 77 stand rejected under 35 U.S.C. § 112, first paragraph, allegedly because the disclosure does not enable expression of functional portions of any heteromeric receptor proteins, other than the variable heavy and variable light chains of immunoglobulins, on the surface of filamentous bacteriophage. In this regard, the

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Office Action alleges that immunoglobulins are not recognized as receptor proteins because they do not directly transduce a cellular signal. The Office Action alleges that the invention does not enable functional fusions with the class of receptors known as ion channels, lack of prior expression of ion channels in immunoglobulins, or bacteriophage ligated forms, and because of structural differences with soluble or bacteriophage ligated forms, and because of absence of guidance in the specification describing expression of such multiple domains of ligand gated ion channels in active form. The Office Action alleges that application of heteromeric binding proteins, other than immunoglobulins, to the invention is not enabled because nucleotide sequences of primers specific to other such receptors are not listed.

Applicant maintains that the specification provides sufficient teachings and guidance to enable those skilled in the art to make and use the invention as claimed. In this regard, Applicant is not claiming any heteromeric receptor expressed on the surface of a cell. Instead, Applicant is claiming prokaryotic cells and bacteriophage expressing functional heteromeric receptors as gVIII fusion proteins on their surface. Teachings and guidance in the application are commensurate in scope with claims as currently amended.

In this regard, teachings and guidance for the expression of functional antibodies and fragments thereof are taught throughout the specification. Additionally, the specification teaches heteromeric receptors other than antibodies and functional fragments thereof, which can be expressed on the

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surface of prokaryotic cells in functional form as gVIII fusion proteins including, for example, T cell receptors, integrins, hormone receptors and transmitter receptors (page 5, line 20-24). The specification additionally teaches, on page 5, line 14-19, that functional heteromeric receptors are those proteins composed of two or more subunits which together exhibit binding activity toward a particular molecule and that it is understood that such receptors, and their fragments, are included within the claimed heteromeric receptors so long as assembly and function of the complex is retained. Moreover, the specification provides sufficient teachings and guidance to enable those skilled in the art to express functional heteromeric receptors on the surface of prokaryotic cells without undue experimentation. The specification exemplifies such teachings with antibody fragment functional heteromeric receptors and, as described above, expressly provides that such methods are applicable to a variety of other heteromeric receptors. Given such teachings, those skilled in the art are able to make and use the claimed invention to produce prokaryotic cell populations expressing functional heteromeric receptors other than antibodies T-cell receptors and functional fragments thereof.

Moreover, those skilled in the art are able to make and test a variety of heteromeric receptors to determine those which assemble into functional heteromeric receptors on the surface of a prokaryotic cell without undue experimentation given the teachings in the specification. For example, page 6, lines 18-34, describes methods for obtaining DNA sequences encoding polypeptides of heteromeric receptors, and page 11, lines 13-33,

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describes general properties of vectors for expressing a population of functional heteromeric receptors, exhibiting binding activity toward a preselected molecule. Furthermore, as described on page 6, lines 24-25, "expression can be performed in any compatible vector/host system." Methods for the isolation of functional heteromeric receptors are described on page 12, line 29, through page 13, line 2 including panning, affinity chromatography and solid phase blotting procedures. These methods test heteromeric receptors based on binding function, thus identifying the functional heteromeric receptors of the claimed invention, and as such are sufficient to enable those skilled in the art to practice the invention as claimed.

In regard to the assertion that expression of antibodies on the surface of a prokaryotic cell does not exemplify heteromeric receptors because antibodies allegedly are not receptors, Applicant respectfully submits that antibodies and functional fragments thereof are heteromeric receptors and provide just one embodiment of the invention as claimed. As described previously, the term "heteromeric receptor" is defined in the specification on page 5, lines 14-23, and "refers to proteins composed of two or more subunits which together exhibit binding activity toward a particular molecule." The definition includes, on lines 20-23, examples of heteromeric receptors with and without signal transduction activity, such as hormone receptors and Fab molecules respectively. Furthermore, this definition is consistent with the definition of "receptor" accepted in the biological arts as demonstrated in Exhibit C, J. Stenesh, Dictionary of Biochemistry and Molecular Biology 2nd

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ed., p.404 (1989) which defines a receptor as "A target site at the molecular level to which a substance becomes bound as a result of a specific interaction." The definition continues with examples of substances which bind receptors and includes "antigens." Antibodies are clearly receptors by this definition since they perform the functional activity of binding a substance and their cognate ligands, antigens, are listed as one such substance. The definition clearly distinguishes signal transduction activity as an optional activity for receptors by using the qualifier "might" in stating that "[t]he binding interaction might trigger a physiological or a pharmacological response". Thus, antibodies, which do not transduce a signal in the form of a physiological or pharmacological response, are receptors. Claims directed toward functional heteromeric receptors therefore, include species other than immunoglobulins in light of that well known in the art and in light of the teachings in the specification.

Finally, in regard to the nucleic acid sequences for heteromeric receptors other than antibodies and T cell receptors, the specification describes methods for making PCR primers sufficient to practice the invention with functional heteromeric receptors. These methods are applicable to essentially all heteromeric receptors for which their encoding sequences are known or which can be determined. Moreover, sequences for heteromeric receptors, methods for obtaining such sequences and the design of PCR primers specific to these sequences are well known in the art. One skilled in the art can therefore make and use the invention with nucleotide sequences encoding full length

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functional receptors, functional fragments of multimeric complexes, or functional fragments of membrane anchored proteins. Methods for making and testing PCR primers, that are specific for heteromeric receptors, are described in the specification. For example, on page 7, line 18 through page 11, line 9, general properties of PCR primers are described. Such teachings are sufficient to enable those skilled in the art to practice the invention as claimed without undue experimentation. Accordingly, Applicant respectfully requests that rejections to claims 1-4, 7, 16-19, 21-29, 31, 32, 66-75, and 77 under 35 U.S.C. § 112, first paragraph be withdrawn.

Claim 24 stands rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Office Action asserts that a DNA sequence is a structural property of a DNA molecule. The Office Action alleges that expression of a DNA sequence as claimed is not equivalent to expression of a DNA molecule.

Claim 24 has been amended to recite that the fusion protein is expressed from a DNA sequence encoding a protein. Accordingly, Applicant respectfully requests that the rejection of claim 24 under 35 U.S.C. § 112, first paragraph be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 3, 70 and 75 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly vague and indefinite. Claim 3 is alleged to be unclear because of a typographical error.

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Claims 70 and 75 are rejected as vague and indefinite allegedly because the criteria for determining at what point similar sequences cease to be substantially the same is unclear.

Claim 3 has been amended to correct the obvious typographical error. Applicant maintains that claims 70 and 75 are sufficiently clear to those skilled in the art to enable the invention to be practiced as claimed. Those skilled in the art would be capable of identifying one sequence as being substantially the same as another sequence based upon, for example, direct comparison of the sequences. A further criterion known to those skilled in the art for determination of substantial similarity between two vectors is comparison of vector function. Moreover, Applicant has exemplified throughout the Examples minor changes in the claimed vector which do not change the overall sequence of the vector and as such are considered to be substantially the same sequence. Accordingly, Applicant requests that rejections under 35 U.S.C. § 112, second paragraph be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 1-5, 7, 26-32, 66-75, and 77 stand rejected under 35 U.S.C. § 103 as allegedly being obvious over Huse et al. (Science 246:1275-1281, 1989), in view of Ladner et al. (WO 88/06630, 1988) and patent no. 5,223,409 (Ladner et al.). The Office Action states that Huse et al. describe the expression of a combinatorial Fab expression library in the intracellular space

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of *E. coli*. Ladner et al. and patent no. 5,223,409 are cited for allegedly describing the expression of a library of potential binding proteins on the surface of bacteriophage, and for describing methods to screen for desired binding characteristics. The Office Action alleges that Ladner et al. describes expression of any protein or antibody domain on the surface of a bacteriophage and asserts that a reasonable expectation of success in expressing Fab molecules on the surface of bacteriophage results from Huse et al., which describes that Fab molecules readily assembled within the environment of *E. coli*, and the secondary publications which describe bacteriophage that also assemble in the *E. coli* environment. The Office Action further alleges that claims 66-75, which require two copies of the gVIII that differ from one another in nucleotide sequence are obvious in light of Example I of Patent no. 5,223,409.

Applicant maintains that the cited references do not render the invention obvious. The current invention claims surface expression of heteromeric receptors containing at least two subunits that self-assemble on the surface of a prokaryotic cell or filamentous bacteriophage. In contrast, Ladner et al. and U.S. Patent No. 5,223,409 describe the expression of a single polypeptide chain on a phage surface. The expression of single polypeptide chains does not teach or suggest the expression and self-assembly of multiple subunits into functional heteromeric receptors as taught and claimed in the above-identified application. The expression of "[a]ny protein or antibody domain," as quoted from Ladner et al. in the Office Action, does

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not include the expression and functional assembly of more than one subunit as claimed in the instant application.

With or without the combination of Huse et al., functional surface expression of heteromeric receptors would not have been obvious because the surface expression of functional heteromeric Fab receptors requires at least a bi-molecular association event between the two or more receptor subunits following extrusion through the membrane. This self-assembly would not have been obvious in light of the single chain antibodies of Ladner et al. and Patent No. 5,223,409 because there was no second subunit for assembly and because the environment on the surface of the cell is significantly different from the environment inside the *E. coli* cytoplasm. Therefore, the methods of Huse et al. could not provide a reasonable expectation of success when combined with Ladner et al. and U.S. Patent No. 5,223,409 to teach or suggest the claimed invention. Accordingly, Applicant respectfully requests that this ground of rejection be withdrawn.

The Office Action further rejects claims 66-75 based on Example I of U.S. Patent No. 5,223,409 allegedly describing a cloning vector containing two genes encoding gVIII.

Claims 66-70 are directed to a vector containing two copies of a filamentous bacteriophage coat protein for the surface expression of a heteromeric receptor polypeptide. Claims 71-75 are directed to a vector containing two copies of a filamentous bacteriophage coat protein for the coexpression of

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two or more DNA sequences encoding polypeptides which form heteromeric receptors. The vector of both groups of claims can express an encoding polypeptide as a fusion protein on the surface of a filamentous bacteriophage or as a soluble polypeptide. U.S. Patent No. 5,223,409, does not teach or suggest a vector with such dual capabilities. Moreover, as U.S. Patent No. 5,223,409 is directed to the expression of single polypeptide chains, this reference similarly does not teach or suggest a vector for the coexpression of two or more inserted DNA sequences for a heteromeric receptors as is claimed in claim 71. Absent such teachings or suggestions, the cited reference cannot render claims 66-75 obvious and withdrawal of the rejection is respectfully requested.

Double-patenting rejections

Claims 16-32 and 68-75 stand provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-33 and 68-75 of copending application serial number 08/470,297. Claims 1-5, 7 and 16-33 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-8, 16-21 and 23-33 of application serial number 08/349,131, now claims 1-32 of U.S. Patent Number 5,871,974. Applicant respectfully requests that these grounds of rejection be deferred until there is an indication of allowable subject matter in the subject application.

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CONCLUSION

In light of the amendments and remarks herein,
Applicants submit that the claims are now in condition for
allowance and respectfully request a notice to this effect.
Should the Examiner have any questions, he is invited to call
Cathryn Campbell or the undersigned agent.

Respectfully submitted,



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